

Modeling DNA conformational transformations on the mesoscopic scales

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The approach for the description of the DNA conformational transformations on the mesoscopic scales in the frame of the double helix is presented. Due to consideration of the joint motions of DNA structural elements along the conformational pathways the models for different transformations may be constructed in the unifying two-component form. One component of the model is the degree of freedom of the elastic rod and another component – the effective coordinate of the conformational transformation. The internal and external model components are interrelated, as it is characteristic for the DNA structure organization. It is shown that the kinetic energy of the conformational transformation of heterogeneous DNA may be put in homogeneous form. In the frame of the developed approach the static excitations of the DNA structure under the transitions between the stable states are found for internal and external components. The comparison of the data obtained with the experiment on intrinsic DNA deformability shows good qualitative agreement. The conclusion is made that the found excitations in the DNA structure may be classified as the static conformational solitons.

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I. INTRODUCTION

The study of the conformational transformations of DNA double helix is the line of understanding the mechanisms of the living systems functioning. Last decade particular attention attracts the conformational transformations of DNA macromolecule, which include the displacements of the structural elements in the frame of double helix with relatively large deviations from equilibrium positions. The amplitudes of these displacements are not small, but on the other hand – not so large to destroy the double helix organization. Such DNA transformations in the frame of double helix we will name as mesoscopic, leaving the term "large-scale" for the displacements of the structural elements that can destroy the helix. The DNA mesoscopic transformations show themselves in the formation of intermediate *A-B* conformations in the complex of DNA TATA-box with proteins [1-4], the motifs of *A*-form in ligand-bound DNA (see [5] and cited therein), the junctions of *B*- and *A*-forms in DNA fragments bound to the protein or drug [6-9], the bistable flexibility of *A*-tract [10-12], the base-pair preopening in oligonucleotide duplex [13], the overstretching of DNA helix under high tension [14,15], and in a number of unusual DNA conformations [16]. In mentioned above conformation transformations the displacements of DNA structural elements are accompanied with the deformation of DNA macromolecule as a whole, but without the destruction of the double helix.

The investigation of the mesoscopic transformations is of great interest because these DNA rearrangements directly connect with the regulation of the genes activity [1,17]. From a complex structure of DNA macromolecule the experimental study of its conformational mobility meets with some obstacles [18]. One of the productive way to understand the conformational resources of the double helix is the use the phenomenological approach to modeling its conformational transformations. The exploring such models as "helix-coil" [19-21] or "elastic rod" [22-26] speeds up and extends the investigations of the conformational properties of the nucleic acids, and allow to interpret a set of experimental data on DNA melting, helix bending and torsion, loop formation and higher order folding. The model approach has definite advantages comparing to various all atoms computational methods. From the large number of atoms in a macromolecule the use of the computational approach is restricted by the fragments of DNA helix not longer than 20 base pairs [27,28]. At the same time under successful model construction the phenomenological approach allows to describe the structural transformations in macromolecules of the real size and with the account of surrounding factors.

For modeling DNA mesoscopic transformations it would be advantageous to use an experience in the modeling of large-amplitude mobility of the structural elements in DNA double helix, and the study of the possibility of the localized excitations realization [29]. On this direction quite a number of models have been constructed (see review [30], collected articles [31] and book [32]). But not all of these studies achieved real results because of the significant simplifications of the models and the difficulties of tacking into account such principle properties of DNA structure, as nucleotide content and sequence.

Recently, a set of the models for the reduced description of the internal mobility of DNA structural elements on the large scales has appeared [33-37]. The authors of this studies divide the atoms of the double helix on the atomic groups – the new "structural" elements of the system, and try to find the potential field which could describe the interactions between them. This is a very complicated task which cannot be resolved for DNA as a whole.

In the present work the another way is proposed. In modeling DNA conformational transformations on the mesoscopic scales the four-mass model approach is used. This approach was developed earlier [38-40] for the description of DNA double helix conformational vibrations. The achieved agreement between theory and experiment in the description of the DNA low-frequency spectra [39,40] show the accordance of the four-mass model to the described mobility of the double helix. It would appear reasonable that the displacements of DNA structural elements with small amplitudes are the precedes of the mesoscopic and large amplitude transformations. It is taken into account also that under double helix transformations the structural elements move jointly along the conformational pathways. Therefore, starting from the four-mass model for DNA internal mobility the models for definite pathways of the double helix transformations are constructed. Such an approach allows us to reduce significantly the degrees of freedom of a system and to choose the adequate potential functions for described force field.

Using the proposed approach the models for the description of DNA conformation transition of $A-B$ type and double helix opening are constructed. It is shown that different conformational rearrangements of the structural elements in the double helix may be described by the unifying two-component model. The accounting of the interrelation between the model components is discussed as an important part of the description of DNA transformations. In the frame of the two-component model the static excitations are found for two types of the conformational transformations of the macromolecule: transition from the ground state to metastable and transition between the equivalent states in the conditions of DNA bistability (for example, $A-B$ equilibrium). The obtained results are compared with the experimental data on DNA deformability.

II. MODEL CONSTRUCTION

The DNA molecule consists of two strands which are formed by the linked phosphate groups and deoxyribose (or sugar) rings. To the sugar rings the nucleic bases are attached. The DNA bases have different content of atoms, that is why the primary structure of a macromolecule is heterogeneous and may be used for writing the genetic information. In the natural conditions DNA strands form the double helix – DNA secondary structure, where the nucleic bases of different strands are connected by hydrogen bonds in the complementary pairs A·T and G·C.

The DNA rearrangements on non-small scales in the frame of the double helix have a character of transitions from one stable state to another [18]. Under conformational transformations the disposition of the structural elements in double helix monomer units changes, and the macromolecule as a whole suffers definite deformation. The form of macromolecule deformation and the type of the conformational state of the double helix are observed in the experimental studies [1-16]. So, for modeling the mesoscopic transformations of DNA double helix it is important that the constructed model will include the components for the description of the internal conformational transformation and the external deformation of macromolecule. For construction the models of definite DNA transformations let us consider the four-mass model approach.

A. Generalized four-mass model

According to approach of four-mass model for the DNA monomer link [38-40] the basic conformational degrees of freedom, which characterize the mobility of the structural elements of a double helix, are the following. First of all, the displacements of the nucleosides (nucleic bases together with sugar rings) as rigid pendulums "suspended" to the backbone (Fig. 1a). Secondly, intranucleoside transformations: the displacements of nucleic bases under the changes in the sugar rings conformation. The third type is the displacements of a nucleotide as a whole (nucleic base + sugar + phosphate group).

For the description of DNA structural dynamics in the approach [38-40] two masses of the pendulum-nucleosides (m) and two masses of the backbone atom groups (m_0) (Fig. 1) were used. The masses of nucleosides have the different values according to the kind of the nucleic base. The backbone masses m_0 include the group of atoms: $\text{PO}_2 + 2\text{O} + \text{C}_5'$ and are identical along the chain. The necessary structure parameters of the model, such as the length of the physical pendulum-nucleosides – l_0 , and the angles of their position in the pair plane – Θ_0 (Fig. 1) calculate from the known double helix conformation. For DNA B-form the calculated parameters of the model are shown in the Table I. As seen, four-mass model takes into account an essential property of the DNA macromolecule – heterogeneity of its monomer content. Really, the model masses and geometrical parameters of the pendulum-nucleosides depend on the nucleic bases contained in its constitution.

Let us consider the possibility of using the four-mass model for description of the mesoscopic transformations of DNA double helix. We will write the expression for the energy of generalized four-mass model without envisaging the

smallness of displacements:

$$E = \frac{1}{2} \sum_{i,n} \left\{ m_0 \dot{\mathbf{R}}_{i,n}^2 + m_i \dot{\mathbf{r}}_{i,n}^2 + U(\mathbf{r}_{i,n}; \mathbf{R}_{i,n}) \right\}. \quad (1)$$

In the expression (1) the summation is made over all monomer links (n) of the double chain ($i = 1, 2$). The radius-vectors $\mathbf{R}_{i,n}(t)$ and $\mathbf{r}_{i,n}(t)$ describe the displacements of the mass centers of the backbone groups and nucleosides, respectively, in each chain. The $\dot{\mathbf{R}}$ and $\dot{\mathbf{r}}$ denote the time derivatives. The function U is the potential energy of conformational transformations of a system.

Taking into account the structural organization of a macromolecule, the potential energy of the n -th monomer link would be presented as:

$$U(n) = U^{(1)}(n) + U^{(2)}(n, n-1) + U^{(3)}(n; n \pm 1). \quad (2)$$

The first term in the sum (2) describes the energy related to the internal rearrangements in n -th monomer of the macromolecule as such. In the four-mass model this energy may be written as:

$$\begin{aligned} U^{(1)} &= U_1^{(1)}[\mathbf{R}_1 - \mathbf{r}_1] + U_2^{(1)}[\mathbf{R}_2 - \mathbf{r}_2] + \\ &+ U_3^{(1)}[\mathbf{r}_1 - \mathbf{r}_2] + U_4^{(1)}[\mathbf{R}_1 - \mathbf{R}_2], \end{aligned}$$

where $U_1^{(1)}$ and $U_2^{(1)}$ are the energies of the nucleoside displacement with the respect to the backbone group in each strand, $U_3^{(1)}$ is the energy of the H-bond stretching in the base pairs, and $U_4^{(1)}$ is the energy of the interaction of the backbone groups of different helix chains. But, at once the term $U_4^{(1)}$ may be omitted because interaction between backbone groups in a monomer link is much less than the same interaction along macromolecule chain (the corresponding distances differ more than twice [18]). The interactions along the backbone chains will be taken into account in another potential terms.

The term $U^{(2)}$ in the sum (2) describes the energy of the interaction along the macromolecule chain. This energy term may be written in the form corresponding to the traditional approach of the elastic rod model with the accounting interactions between the nearest neighbors. The view of the term $U^{(2)}$ would be concretized for definite coordinates of the conformational rearrangements.

The term $U^{(3)}$ describes the energy of the interrelation between the intermonomer transformations (conformational changes), and the changes of the configuration of the helix as a whole (deformation of the macromolecular chain). The term $U^{(3)}$ is important under the consideration of the mesoscopic displacements of the macromolecule structural elements, because DNA structure is relatively soft, and under the change of the monomer configuration the position of monomer link in a macromolecule chain changes also [18].

The energy expression (1,2) is sufficiently complicated for the direct use. Firstly, the vector character of the displacements which requires the construction of the corresponding force field for the macromolecule. Secondly, the heterogeneity of the energy terms, that makes the analytical study practically impossible.

But, as known [18,25,27,41-47] under rearrangements of DNA structure in the frame of the double helix the displacements of the structural elements of the monomer link are interdependent, and DNA structural elements move jointly along the definite conformational pathways. Let us take this fact into account and consider the model constructing for the basic conformational transformations of DNA double helix: the conformational transition of A - B type and the helix opening.

B. Conformational transitions

Under modeling DNA conformational transitions let us introduce the displacements of the center of masses of the pair of nucleosides (\mathbf{r}_p) and the center of masses of the backbone groups (\mathbf{r}_q), as well as the displacements of the nucleosides with respect to each other in the monomer link (δ), and the same for the backbone masses (Δ):

$$\begin{aligned} \mathbf{r}_p &= \frac{m_1 \mathbf{r}_1 + m_2 \mathbf{r}_2}{m_p}, & m_p &= m_1 + m_2; \\ \delta &= \mathbf{r}_1 - \mathbf{r}_2, & \mu_p &= m_1 \cdot m_2 / m_p, \end{aligned} \quad (3)$$

where m_p is the mass of pair of the nucleosides in the monomer link, and μ_p is the reduced mass of the nucleosides. Accordingly, for the backbone masses we have:

$$\begin{aligned} \mathbf{r}_q &= \frac{1}{2} (\mathbf{R}_1 + \mathbf{R}_2), & m_q &= 2m_0; \\ \Delta &= \mathbf{R}_1 - \mathbf{R}_2, & \mu_q &= m_0/2. \end{aligned} \quad (4)$$

In the designations (3) and (4) the expression for the n-th item of the kinetic energy of a system takes the form:

$$K_n = \frac{1}{2} \left\{ m_p \dot{\mathbf{r}}_p^2 + m_q \dot{\mathbf{r}}_q^2 + \mu_p \dot{\delta}^2 + \mu_q \dot{\Delta}^2 \right\}. \quad (5)$$

For the further advance it is useful to put out the displacements of the mass center of a monomer link (\mathbf{R}) and displacements of the mass center of a pair with respect to the backbone masses (\mathbf{r}):

$$\begin{aligned} \mathbf{R} &= \frac{m_p \mathbf{r}_p + m_q \mathbf{r}_q}{M}, & M &= m_1 + m_2 + 2m_0; \\ \mathbf{r} &= \mathbf{r}_p - \mathbf{r}_q, & m &= m_p \cdot m_q / M. \end{aligned} \quad (6)$$

Here M and m are the mass and reduced mass of a monomer link, respectively. Taking into account (6) an expression for the kinetic energy takes the following form:

$$K = \frac{1}{2} \sum_n \left\{ M \dot{\mathbf{R}}_n^2 + m \dot{\mathbf{r}}_n^2 + \mu_p \dot{\delta}_n^2 + \mu_q \dot{\Delta}_n^2 \right\}. \quad (7)$$

Notice, the expression (7) can be simplified some more. At the description of the dynamics of conformational transitions not all terms of the kinetic energy are equally important. As was mentioned above, the potential energy associated with the last term in the kinetic energy (7) may be omitted ($U_4^{(1)} \sim 0$). Thus, from the point of classical mechanics Δ is the cycle coordinate, and it can be ignored here. So, it is possible to neglect the last term in the expression (7).

Let us take into account also, that in such structural transformations as conformational transitions between the forms of *B*- and *A*- families of a double helix, the nucleic bases in the pair displace together without significant mutual shifts. In any case, under conformational transition both in the initial and in the final helix forms the bases remain in a configuration of a complementary pair [5,18,41-43,47]. So, we will assume that under DNA conformational transitions it is true: $\delta \approx \dot{\delta} \approx 0$. Therefore, an expression for the model kinetic energy for the description of conformational transitions can be written as the following:

$$K_{tr} = \frac{1}{2} \sum_n \left\{ M \dot{\mathbf{R}}_n^2 + m \dot{\mathbf{r}}_n^2 \right\}. \quad (8)$$

The kinetic energy in the form (8) remains still sufficiently complicated for the modeling. And, as the last step in model construction, let us take into account that in the conformational transformations of the macromolecule the masses M and m have the primary directions of the displacements. As it is known, under the conformational transitions of *A-B* type the mass center of DNA monomer link has the most displacement in the plane which is orthogonal to the helix axis [18,41-43]. Thus, for the degree of freedom of the monomer mass center it is convenient to pass to the displacements in the plane *XOY* (we put the helix axis along *OZ*, Fig. 1). In this case we have:

$$M \dot{\mathbf{R}}^2 = M \dot{\Upsilon}^2 + I \dot{\varphi}^2,$$

where Υ and φ are the displacement and the angle of rotation of the link in the plane *XOY*, $I = I_{0Z}$ is the moment of inertia of the monomer link with respect to a helix axis.

The necessity of taking into account the displacement on Υ and torsion on φ simultaneously is determined by the concrete conditions of the transition. Both types of deformation are observed in the experiment studies [5,18]. Under definite conformational transitions these degrees of freedom change in a correlative character to minimize the distortion of base pair stacking. The including in the model both degrees of freedom do not cause the difficulties. For the purposes of the present study under description of *A-B* transition we will use one coordinate - Υ to denote this type of the transformation.

In its turn it is also known [18,43,47,48], that under conformational transitions the base pairs displace transversely to the helix axis, along the axis *OX* (Fig. 1b). Thus, for the component \mathbf{r} it is expedient to pass to the displacement along the trajectory of the mass center motion: $\mathbf{r} \rightarrow u$.

In such a way an expression for the kinetic energy of the $A-B$ transition in terms of Υ and u can be written in the scalar form:

$$K_{tr} = \frac{1}{2} \sum_n \left\{ M \dot{\Upsilon}_n^2 + m \dot{u}_n^2 \right\}. \quad (9)$$

Under constructing the kinetic energy of the system one fact has attracted the attention at once. After passing in the kinetic energy to the description of the joint motions (beginning from the expression (7)) the appeared mass coefficients don't depend on the heterogeneity of the monomer content of DNA macromolecule. The calculated values of the masses are shown in the Table II for A-T and G-C pairs.

The potential energy for the conformational transition in the selected coordinates consists of the energy of helix bending (external component) and the energy of base pair displacements (internal component).

The energy term $U^{(1)}$ in expression (2) in this case comes to the energy of the pair displacements relative to the backbone. These displacements occur due to the changing in the sugar ring conformation [18,41,43,47,48], and the potential energy along the coordinate u corresponds to the transition from one sugar form to another. We will describe this energy by the function $\Phi[u]$.

The term $U_3^{(1)}$ in expression (2) which describes the energy of the H -bonds stretching in the base pairs has to be omitted because the conformational transformations of $A-B$ type, as was mentioned above occur without significant change of the distance between nucleosides mass centers ($\delta \approx 0$).

The potential energy of the interaction along the macromolecule chain (term $U^{(2)}$ in expression (2)) includes the energy of the bending on the component Υ which is bound to have the view akin to the bending energy of the elastic rod, and the energy of the change of pairs stacking interactions (displacement u).

Therefore, the expression for the potential energy for the description of the dynamics of the conformational transitions of DNA macromolecule takes the form:

$$U_{tr} = \frac{1}{2} \sum_n \left\{ k_{\Upsilon} [\Upsilon_n - \Upsilon_{n-1}]^2 + k_u [u_n - u_{n-1}]^2 + \Phi[u_n] + W[u_n; \Upsilon_{n\pm 1}] \right\}. \quad (10)$$

In the expression (10) k_{Υ} and k_u are the elastic constants of the interactions along the macromolecular chain for bending and pair displacement components, respectively.

The term with the function W describes the interrelation between the base pair displacement in n -th monomer and the corresponding displacement of the n -th monomer with respect to $(n-1)$ -th and $(n+1)$ -th monomers (the term $U^{(3)}$ in the expression (2)). Here: $\Upsilon_{n\pm 1} = [\Upsilon_{n+1} - \Upsilon_n] + [\Upsilon_n - \Upsilon_{n-1}] = [\Upsilon_{n+1} - \Upsilon_{n-1}]$.

The energy expression (9,10) may be used for modeling the dynamics of DNA conformational transitions. It is important to note that owing to passing to the description of joint motions, the mass coefficients in kinetic energy became non-sensitive to the nucleotide heterogeneity in DNA. Moreover, the potential energy of the conformational transition dynamics became also non-sensitive to DNA nucleotide content. The effect of DNA heterogeneity may reveal only in some sensitivity of model elastic constants (k) to the nucleotide sequence in macromolecule because of known sensitivity to the sequence of the potential energy of interactions along the DNA chain [18]. These properties of the model are in common agreement with the known data about non-sensitivity of DNA $A-B$ transitions to the nucleotide content [41,48].

C. Opening

Other structural transformation that has attracted considerable interest in DNA physics is the pair opening in DNA double helix. This process offers the conformational transformation, as a result of which the hydrogen bonds in the complementary pairs disrupt, and the nucleic bases turn out from the double helix [18].

It is considered [27,46] that the most probable trajectory for double helix opening is the turning of bases of the pair around backbone chains to the sides of the helix grooves (so called "opening", the direction of rotation on the angles θ_1 and θ_2 , Fig. 1b). The other possible pathway connected with the stretching of base pair along the H-bonds (OY axis on Fig. 1b, "stretching") is assumed as less probable because of known strong rigidity of the backbone chains in the direction of OY axis [42]. The "stretching" process can realize under the temperature increase in the conditions of melting. The modeling of the base pair stretching in double helix was made in a number of works [30,49-52] with the help of one-component model. In the present study the "opening" trajectory will be considered, as the most probable in the natural conditions where the mesoscopic transformations occur.

Let us consider the form of kinetic energy for description of the double helix opening. In the four-mass model (1,2) we will introduce the displacements of mass centers of the nucleosides with respect to the backbone, and the displacements of mass centers of the nucleotides as a whole. For the displacements of masses in the n -th link of the i -th DNA strand we will write the following equations:

$$\begin{aligned}\wp_i &= \frac{m_i \mathbf{r}_i + m_0 \mathbf{R}_i}{M_i}, & M_i &= m_i + m_0; \\ \rho_i &= \mathbf{R}_i - \mathbf{r}_i, & \mu_i &= m_i \cdot m_0 / M_i,\end{aligned}\tag{11}$$

where M_i and μ_i are total and reduced masses of the nucleotide in the i -th strand.

Since the main process in the opening transformation is the extension the H-bonds in the base pair, it may be assumed that under helix opening the nucleosides remain rigid. We will consider that in DNA opening the mobility of the nucleosides is brought to the turnings as a whole around the backbone. Thus:

$$\dot{\rho}_i^2 \longrightarrow l_i^2 \dot{\theta}_i^2,\tag{12}$$

where l_i is the reduced length of the pendulum-nucleoside and θ_i is the angle of its deviation from the equilibrium state (Fig. 1b).

Under the conditions (12) the kinetic energy of a system takes the form:

$$K = \frac{1}{2} \sum_{i,n} \left[M_i \dot{\wp}_{i,n}^2 + \mu_i l_i^2 \dot{\theta}_{i,n}^2 \right].\tag{13}$$

The expression (13) remains still complicated for the modeling of the DNA opening. Let us pass to the consideration of the joint motions of the structural elements in the double helix link. With this purpose we will single out the displacements of the mass center of both nucleotides (mass center of monomer link) and the relative displacements of nucleotides in the link. These displacements and the corresponding expressions for the masses have the form:

$$\begin{aligned}\mathbf{R} &= \frac{M_1 \wp_1 + M_2 \wp_2}{M}, & M &= M_1 + M_2; \\ \xi &= \wp_1 - \wp_2, & \mu &= M_1 \cdot M_2 / M.\end{aligned}\tag{14}$$

Let us introduce also the joint turnings of the nucleosides:

$$\begin{aligned}\Omega &= \frac{J_1 \theta_1 - J_2 \theta_2}{J}, & J &= J_1 + J_2 \quad (J_i = \mu_i l_i^2); \\ \sigma &= \theta_1 + \theta_2, & j &= J_1 \cdot J_2 / J.\end{aligned}\tag{15}$$

Here the parameters J and j have a meaning of the joint and relative inertia moments of the nucleosides in the pair. At writing (15) it was taken into account, that the angles θ_1 and θ_2 are disdirective (Fig. 1b). The angle σ correspond to the known parameter "opening" in the classification of DNA transformations [53].

Taking into account the expressions (14) and (15) the kinetic energy of the opening can be presented as:

$$K_{op} = \frac{1}{2} \sum_n \left\{ M \dot{\mathbf{R}}_n^2 + \mu \dot{\xi}_n^2 + J \dot{\Omega}_n^2 + j \dot{\sigma}_n^2 \right\}.\tag{16}$$

The values of the parameters for the kinetic energy (16) are calculated and adduced in the Table III. It is significant that these parameters are practically independent from the kind of DNA pair. Thus, as in the case of the description of conformational transitions, both for helix opening the kinetic energy of the heterogeneous macromolecule assumes the homogeneous form after passing to the joint motions of the structural elements.

Then, for further simplification we will take into account that in the opening process the motions of the structural elements take place along the definite pathway. We will presume the uniform distribution of energy among the moved nucleosides, and in the wake of [27,46] that the opening occur in such way that: $\theta_1 \approx \theta_2$ and $|\Omega| \ll |\sigma|$. So, we will suppose that: $\Omega \sim \dot{\Omega} \sim 0$.

It is also known that when the base pair opens to the side of the helix groove, the monomer link as a whole displaces, and the macromolecule bends [44-46]. On this way the nucleotides in the pair displace jointly, that is corresponded to: $\wp_1 \approx \wp_2$, $|\xi| \ll |\mathbf{R}|$, and $\mathbf{R} \rightarrow Y$, where Y is the coordinate of the displacement to the side of the helix grooves (Fig. 1b).

Thus, an expression for kinetic energy of the double helix opening transformations acquire the two-component form:

$$K_{op} = \frac{1}{2} \sum_n \left[M \dot{Y}_n^2 + j \dot{\sigma}_n^2 \right]. \quad (17)$$

The expression for potential energy for the opening pathway may be presented in the form which looks like the expression (10):

$$U_{op} = \frac{1}{2} \sum_n \left\{ k_Y [Y_n - Y_{n-1}]^2 + k_\sigma [\sigma_n - \sigma_{n-1}]^2 + \Phi[\sigma_n] + W[\sigma_n; Y_{n\pm 1}] \right\}. \quad (18)$$

In the expression (18) k_Y and k_σ are the elastic constants of the interaction along the chain, $\Phi[\sigma]$ - the potential energy of the pair opening which also includes the nucleoside turning around the backbone chains, and the term W describes the energy of the interrelation between the components σ and Y .

The shape of the potential $\Phi[\sigma]$ must allow for the description of transition from the ground state of the double helix to the metastable state. Considering the form of the potential $\Phi[\sigma]$ it must be taken into account that on the pathway of opening the interaction of the opened bases with surrounded water have lead to the formation a set of metastable states of the base pair with molecules of water. Such states (preopened) have been recently found in the quantum-mechanical calculations [54,55], and observed in the experiment [13]. These results show that the double helix opening is the stage-by-stage process, and the potential $\Phi[\sigma]$ has bistable (or more correctly, multistable) form. In the case of the description of the transition from a close state of the double helix to the preopened one the potential $\Phi[\sigma]$ must have the shape of double-well function.

When modeling the potential energy of DNA opening it is important to allow the dependence of the energy of the pair opening on the kind of a pair (the difference in hydrogen bonding of A·T and G·C). In other words, in the case of opening the energy $\Phi[\sigma]$ is sensitive to the base pair content in DNA.

III. UNIFYING MODEL FOR DNA INTERNAL MOBILITY ON THE MESOSCOPIC SCALES

As it is seen from the results of the previous section of this work, the relatively simple two-component models can be constructed for description of various DNA transformations in the frame of double-helical state. The models for different DNA mesoscopic rearrangements are very similar. They include the external component which is the degree of freedom of the elastic rod, and the internal component which is the characteristic coordinate of structural transformation. This is the basic construction that may be modificate by including the additional terms - components of both types. Let us write the expression for the energy of DNA mesoscopic transformation in the unifying form:

$$E = \frac{1}{2} \sum_n \left\{ M \dot{R}_n^2 + k_1 [R_n - R_{n-1}]^2 + m \dot{r}_n^2 + k_2 [r_n - r_{n-1}]^2 + \Phi[r_n] + W[r_n; R_{n\pm 1}] \right\}. \quad (19)$$

In the expression (19) R and r are the degrees of freedom of external and internal components, respectively, M and m - the full and reduced monomer masses, k_1 and k_2 - the elastic constants of the interactions along the macromolecular chain for external and internal components.

The function $\Phi[r]$ describes the potential energy of the internal subsystem on the pathway of a conformational transformation from one stable state to another. Hence, it must have the shape of the double well (Fig.2). The form of the double well is usually known from the experimental data. For the conditions when one of the helix form is more stable (for example at the physiological conditions the most stable is the B-form of the double helix [18]) the function $\Phi[r]$ must be taken in the non-symmetric view with two non-equivalent stable states: ground and metastable (Fig. 2a). That is true both for the conformational transitions such as $A \rightarrow B$, and for the transition in the preopened state. If the conformational transition takes place under equilibrium of the states (for example in the interval of $A \rightarrow B$ equilibrium), the function $\Phi[r]$ must have the symmetric view with two equivalent states (Fig. 2b).

The term W reflects the energy of the interrelation between the components, and may be written in the form:

$$W = \chi F[r_n] \left\{ R_{n+1} - R_{n-1} \right\}. \quad (20)$$

Here χ is the coefficient, the potential function $F(r)$ describes the change in the interrelation energy under the transition of the internal component from one stable state to another. By its physical meaning the potential $F(r)$ is the function that increases from the ground state of the system and decreases near the another stable state. In the case of the description of the transition between the equilibrium states this function must have the symmetric form in accordance to physical equivalence of the states. A sample view of this potential function is shown in Fig. 2a and 2b..

The two-component models of type (20) were used for modeling the transformations of bistable chains of different nature. Firstly such model was used under study of the dynamical properties of the systems with H-bonds [56,57], where the bistable chains with equivalent stable states were considered. The two-component model of bistable macromolecule with non-equivalent stable states was introduced for the study of the nonlinear dynamics of local $A-B$ transitions in DNA [58-61]. The same models were used for the description of DNA melting [62], and the nonlinear dynamics of the endothermic transitions [63].

Let us pass to the continuum approximation, that is frequently used in analytic studies of models. In this case it is supposed that conformational excitation embrace some piece of the macromolecule chain which is much larger than the chain step. In the continuum approximation the expression for the energy (19) may be written in the form:

$$E = \int \frac{dz}{2h} \left[M \left(\dot{R}^2 + s_1^2 R'^2 \right) + m \left(\dot{r}^2 + s_2^2 r'^2 \right) + \Phi(r) + 2\chi h F(r) R' \right], \quad (21)$$

where the expression for the interrelation energy (20) was also taken into account. In the expression (21) $R = R(z, t)$ and $r = r(z, t)$, R' and r' are the derivations on z , $s_1^2 = k_1 h^2 / M$ and $s_2^2 = k_2 h^2 / m$.

Notice, when modeling DNA conformational transformations the sensitivity of the elastic constants to the nucleotide sequence was not considered. Really, the elastic constant k_2 (and to some extent k_1) reflect the value of stacking interactions between the neighbor pairs in the helix. In its turn the stacking depends on the kind of the interacting pairs (see Refs. [18,27,48] and the references therein). This sensitivity of the elastic constants has an effect on the form of the fine structure of conformational excitation, and can be the object of special consideration under study of such effects on the quantitative level.

The equations of motion for two-component excitation with the energy (21) have the form:

$$\ddot{R} = s_1^2 R'' + \chi_1 \frac{dF}{dr} r'; \quad (22)$$

$$\ddot{r} = s_2^2 r'' - \frac{1}{2m} \frac{d\Phi}{dr} - \chi_2 \frac{dF}{dr} R', \quad (23)$$

where $\chi_1 = \chi h / M$ and $\chi_2 = \chi h / m$ - the constants of the interrelations.

The equations (22,23) describe the dynamics of the two-component lattice. It is very much the same that the dynamics of one-dimensional molecular crystal [64]. The significant distinction is the including the terms with coefficient χ . As was mentioned above, the interrelation between the components for such "soft" lattice as DNA macromolecule have been taken into account because of direct evidences of the experiment.

For better understanding the role of interrelation let us consider the dynamics of two-component model (21) in the neighborhood of its ground state. For the small deviation from the ground state: $r = r_0 + \xi$, $\xi \ll r_0$ and $R = \rho \ll r_0$ the expressions for the potential functions may be written as: $\Phi \approx a_0 \xi^2$ and $F \approx b_0 \xi$, where $a_0 = \frac{1}{2} \frac{d^2 \Phi}{dr^2} |_{r_0}$, and $b_0 = \frac{dF}{dr} |_{r_0}$ are the first nonzero terms in the potential expansions on ξ .

The equations of motion (22,23) for the small deviations from the ground state have the form:

$$\ddot{\rho} = s_1^2 \rho'' + \chi_1 b_0 \xi'; \quad (24)$$

$$\ddot{\xi} = s_2^2 \xi'' - \frac{1}{m} a_0 \xi - \chi_2 b_0 \rho'. \quad (25)$$

We will find the decisions of the equations (24,25) in the form of oscillating waves: $\xi = \xi_0 \exp i(\omega t - kz)$ and $\rho = \rho_0 \exp i(\omega t - kz)$. After the wave substitution the equations (24,25) lead to the dispersion equation which may be written as:

$$(\omega^2 - s_1^2 k^2)(\omega^2 - s_2^2 k^2 - 2a_0/m) = k^2 b_0^2 \chi_1 \chi_2. \quad (26)$$

For very small wave vector k ($k^2 \sim 0$) from (26) the two limit frequencies follow: $\omega^2 \approx \omega_0^2 = 2a_0/m$ and $\omega^2 \approx 0$. Thus, in the two-component system (21) we have two type of phonon vibrations. One, with the limit frequency

$\omega_0 = \frac{1}{m} \frac{d\Phi^2}{dr^2} \big|_{r_0}$ - optical branch, that determines the dynamics of the internal component. Second type, with the $\omega \rightarrow 0$ under $k \rightarrow 0$, is the acoustic branch.

The optical branch correspond to the definite optical vibration of the double helix, considered in the linear four-mass model [38-40]. That may be used for more precise selection of the actual degrees of freedom for modeling the mesoscopic mobility, and the evaluation of the parameters of the potential functions.

For small k (k^3 and $k^4 \sim 0$, the quadratic approximation) the expression (26) is equivalent to the following:

$$(\omega^2 - c_1^2 k^2)(\omega^2 - c_2^2 k^2 - \omega_0^2) = 0, \quad (27)$$

where $c_1^2 = s_1^2 - s_*^2$ and $c_2^2 = s_2^2 + s_*^2$, $s_*^2 = b_0^2 \chi_1 \chi_2 / \omega_0^2$.

So, in the quadratic approximation for the dispersion law the analyzed system is the same that is true for usual two-component lattice [64] but with the force constants c_1 and c_2 . The constants include the contribution of the energy of interrelation (s_*). As seen from their values the interaction of the sublattices leads to the softening of the external sublattice - the degrees of freedom of the elastic rod, and to the greater rigidity of the internal sublattice. Notice that the effect of the component interrelation is larger than the frequency of the corresponding conformational vibration is lower. As known (see [38-40] and reference therein), the frequency of DNA conformational vibrations are sufficiently low ($< 100 \text{ cm}^{-1}$). So, the effect of the component interrelation is important, and must be taken into account under the modeling DNA mesoscopic transformations.

IV. STATIC STATES OF THE TWO-COMPONENT MODEL

In this section we will consider the static states of the unifying model (21), which may be compared with experiment to demonstrate the correctness of the approach. To the static states we will assign the stable static states of the system and the static excitations which can be stable under some conditions. The stable static excitations of the system may be observed as static deformations of the real macromolecule. So, let us determine the static states of the two-component model (21).

For more general character we will study the static states of the system without definition of concrete expressions for the potential functions. In accordance with the shape of the potentials we will assumed that the potential energy of the system will have three extremums: two minimums (r_0, r_2) and one maximum (r_1) between them. In the ground state $r = r_0$ (B-form for DNA) we will consider $\Phi(r_0) = F(r_0) = 0$. In the metastable state ($r = r_2$) $\Phi(r_2) \neq 0$, $F(r_2) \neq 0$ (Fig. 2a). For the conditions when the macromolecule have two equivalent stable states (Fig. 2b) the function $F(r)$ for r_2 give $F(r_2) = 0$.

For providing of the bistable form of the model energy it is necessary to satisfy the definite conditions for the extremum points [65]:

$$\Phi(r_{1,2}) \geq \frac{\chi^2}{k_1} F^2(r_{1,2}), \quad (28)$$

that is an inequality for r_1 state always, and for r_2 state is inequality in the case of the non-equivalent states and - equality for the case of equivalent states.

A. Static excitation in the macromolecule with metastable states

Let us find the static excitations of the macromolecule with metastable states in the monomer link. We will assume: $r = r(z)$ and $R = R(z)$, and $R'(z) = \tau/h$. Here the value $\tau(z)$ is coined for the determination of the macromolecule deformation on the external component (torsion or bending, in dependence of concrete model). The equations described the static excitations follow from the Eqs. (22,23) of the system:

$$R'' + \tilde{\chi}_1 \frac{dF}{dr} r' = 0; \quad (29)$$

$$r'' - \frac{1}{2\kappa} \frac{d\Phi}{dr} - \tilde{\chi}_2 \frac{dF}{dr} R' = 0. \quad (30)$$

In the Eqs. (28,29) $\tilde{\chi}_1 = \chi/k_1 h$, $\tilde{\chi}_2 = \chi/k_2 h$ and $\kappa = k_2 h^2$.

After one time integration of the Eq. (29) we obtain:

$$R' + \tilde{\chi}_1 F(r) = 0, \quad (31)$$

where the constant of integration put to zero according to the initial conditions for the stable state. The deformation of the external component of the macromolecule chain may be written from the Eq. (31) as:

$$\tau = -\frac{\chi}{k_1} F(r). \quad (32)$$

As seen from expression (32) the deformation of the chain in the model is proportional to the function $F(r)$.

After substitution the expression for R' in the Eq. (30) and one time integration we obtain the equation for the internal component:

$$r'^2 - \frac{1}{\kappa} \Phi(r) + \tilde{\chi}_1 \tilde{\chi}_2 F^2(r) = C,$$

which may be rewritten in the form:

$$r'^2 + Q(r) = 0. \quad (33)$$

The equation (33) have the view of the energy of the mechanical system with the potential energy: $Q(r) = -\frac{1}{\kappa} \Phi(r) + \tilde{\chi}_1 \tilde{\chi}_2 F^2(r) - C$.

The solution of the Eq. (33) may be found as the conversion of the integral

$$\int_{r(0)}^{r(z)} \frac{du}{\sqrt{-Q(u)}} = z. \quad (34)$$

The view of the effective potential $Q(r)$ is determined by the concrete form of the potential functions Φ and F . When fulfilling the condition (28) the effective potential $Q(r)$ have the form of a double hump (see Fig. 3a).

Let us consider the possible solutions of the equation (34). We will find the excitations with a restricted trajectory and the asymptote of one of the stable states of the system because such excitations are the most stable in the real conditions. For the potential $Q(r)$ with two non-equivalent humps we will search the excitation with the asymptote of the metastable state r_2 (Fig. 3a). In this case it is convenient to present the polynom $Q(r)$ in the form:

$$Q(r) = -Q_m^2 (r_2 - r)^2 (r - \eta_1)(r - \eta_2). \quad (35)$$

In the expression (35) Q_m^2 is the combination of the model parameters, r_2 , η_1 and η_2 ($\eta_1 < \eta_2 < r_2$) are the zeros of the polynom $Q(r)$ with the meaning $C = -\frac{1}{\kappa} \Phi(r_2) + \tilde{\chi}_1 \tilde{\chi}_2 F^2(r_2)$ for the boundary conditions of the metastable state ($r = r_2$ and $r'_2 = 0$). We will interest in the excitations with the trajectory restricted by the interval: $\eta_2 \leq r \leq r_2$ (see Fig. 3a).

For the polynom $Q(r)$ in the form (35) the integral equation for the function $r(z)$ have the form:

$$\int_{\eta_2}^{r(z)} \frac{du}{(r_2 - u) \sqrt{(u - \eta_1)(u - \eta_2)}} = \pm Q_m z. \quad (36)$$

The integral (36) have the table view. After integration we obtain the following relation:

$$\ln \left\{ \frac{1}{(r_2 - r)(\eta_2 - \eta_1)} \left[\sqrt{(r_2 - \eta_1)(r - \eta_2)} - \sqrt{(r_2 - \eta_2)(r - \eta_1)} \right]^2 \right\} = \pm Q_m z \sqrt{(r_2 - \eta_2)(r_2 - \eta_1)}.$$

Or, after rewriting:

$$\begin{aligned} & \exp(q_m z) (r_2 - r) (\eta_2 - \eta_1) \\ &= \left[\sqrt{(r_2 - \eta_1)(r - \eta_2)} - \sqrt{(r_2 - \eta_2)(r - \eta_1)} \right]^2, \end{aligned} \quad (37)$$

where $q_m = \pm Q_m \sqrt{(r_2 - \eta_2)(r_2 - \eta_1)}$.

For convenience let us designate: $r_a = r_2 - \eta_2$ and $r_b = \eta_2 - \eta_1$. The values r_a and r_b reflect the form of the potential $Q(r)$ (Fig. 3a). Their substitution to the Eq. (37) lead to the expression:

$$(r_2 - r) [r_b \exp(q_m) + 2r_a + r_b] - 2r_a(r_a + r_b) \\ = 2\sqrt{r_a(r_a + r_b) [(r_2 - r)^2 - (r_2 - r)(2r_a + r_b) + r_a(r_a + r_b)]}. \quad (38)$$

After raising to the second power of the whole expression (38) it is easy to obtain the form of the internal component of the static excitation:

$$r(z) = r_2 - r_{\text{ex}}(z), \quad (39) \\ r_{\text{ex}}(z) = \frac{2r_a(r_a + r_b)}{r_b \text{ch}(q_m z) + 2r_a + r_b}.$$

As seen, at $z \rightarrow 0$ (the middle point of the excitation) $r_{\text{ex}} \rightarrow r_a$ and $r(z) \rightarrow \eta_2$. At $z \rightarrow \infty$, $r_{\text{ex}} \rightarrow 0$ and $r(z) \rightarrow r_2$ (Fig. 3b).

The external component of the excitation according to the Eq. (31) have the form:

$$\tau_{\text{ex}}(z) = -\frac{\chi}{k_1} F[r_2 - r_{\text{ex}}(z)]. \quad (40)$$

At $z \rightarrow \infty$, $r_{\text{ex}} \rightarrow 0$, $\tau_{\text{ex}} \rightarrow \tau_2$ and at $z \rightarrow 0$, $r_{\text{ex}} \rightarrow r_a$, $\tau_{\text{ex}} \rightarrow \tau_a = -\frac{\chi}{k_1} F[r_2 - r_a]$, where $0 > \tau_a > \tau_2$.

Thus, as seen from the Eqs. (39,40) the static excitation has the form of the bell with the width that is proportional to $q_m^{-1} \sim (r_a^2 + r_a r_b)^{-\frac{1}{2}}$ and the height $-r_a$. At the middle point of the excitation the components have the values that are close to the same for the ground state (Fig. 3b). On the edges of the excitation the components have the values of the metastable state.

The obtained results may be used for comparison with the observed static deformation of the macromolecule. The set of data on the static conformational deformation in DNA was published recently. So, in the work [66] it was found the structure of DNA-protein complex. The reconstruction of DNA structure in this complex [5,67] show that protein has induced $B \rightarrow A$ transition in DNA, and the DNA fragment is bent and looked as the bell. Besides that, the conformation of the double helix in the center of deformation is close to ground state (B -form), and on the edges - to A -form.

Notice, that the static excitation (39,40) is commonly agree with the observed form of DNA deformation. As in experiment [5,66,67] the obtained static excitation has the maximum deformation on the edges of the fragment ($\tau = \tau_2$), and the minimum - at the central part ($\tau = \tau_a$, which $\tau_2 < \tau_a < 0$) (Fig. 3b). It is also important, that the theory gives for the internal component the conformation of the metastable state on the edges of the excited fragment, and the conformation closed to the ground state for the central part. That is also in accordance with the experiment [5,66,67].

B. Static excitation in the macromolecule with equivalent states in the monomer link

Let us consider the static excitations of the two-component chain (21) with equivalent states in the monomer link. As in previous case the form of the excitation for internal and external components is determined by the Eqs. (32-34). For the equivalent states in the monomer the effective potential $Q(r)$ in the Eq. (33) has the shape of the double hump with equal humps (Fig. 4a). We will find the solution of the Eq. (34) for the boundary conditions of the stable states ($r \rightarrow r_0$ or r_2 and $r' \rightarrow 0$ when $z \rightarrow \infty$). For these conditions the constant C in the polynom $Q(r)$ is equal to 0. It is convenient to present the potential $Q(r)$ in the form:

$$Q(r) = -Q_e^2(r_2 - r)^2(r - r_0)^2, \quad (41)$$

where Q_e^2 is the combination of the model parameters.

The substitution of the expression (41) into the Eq. (34) and integration gives the relation:

$$\frac{1}{(r_2 - r_0)} \ln \left| \frac{r_2 - r(z)}{r_0 - r(z)} \right| = \pm Q_e z. \quad (42)$$

After rearrangement of the Eq. (42) we obtain the expression for the internal component of the excitation in the following form:

$$r(z) = r_e + r_d \text{th}(q_e z), \quad (43)$$

where $r_e = (r_2 + r_0)/2$ ($r_e = r_1$ for symmetric bistable potential Φ), $r_d = (r_2 - r_0)/2$ and $q_e = \pm r_d Q_e$.

As seen from Eq. (43) at $z \rightarrow \pm\infty$, $r(z) \rightarrow r_2$ or r_0 in dependence on the sing of q_e . At $z = 0$, $r(z) = r_e$ (Fig. 4b). The width of the excitation is proportional to $(r_d)^{-1}$.

For external component in accordance with Eq. (32) and the form of the potential function $F(r)$ in the case of equivalent states (Fig. 2b) we have the following: when $z \rightarrow \pm\infty$ then $\tau \rightarrow 0$, and $\tau(0) = \tau_e = -\frac{\chi}{k_1} F[r_e]$ at $z = 0$ (Fig. 4b). Thus the external component has another form in compare with the case of non-equivalent states. In the central part of the macromolecule fragment the deformation have the maximum value, and on the edges of the excitations the deformation is absent.

These results may be compared with the data of molecular images of the protein-induced A - B transformation of DNA [5]. In the work [5] the structure of the crystal DNA-protein complex [68] was reconstructed in all-atom presentations for DNA fragment. As seen from the data of [5], the DNA portion in the complex is in the B -form, but free portion of DNA remains in the A -form. At the A - B junction DNA macromolecule bent [5]. The observed DNA transformation is in agreement with the results of the present modeling. As in experiment, the static excitation for the DNA with equivalent states is caused by the transition between the forms of the double helix, and has the maximum of macromolecule deformation at the center of A - B junction (Fig. 4b).

The obtained results have also a good accordance with the data on intrinsically bent DNA [10,11]. As considered, the DNA fragments with the homogenic sequence of A-T pair (A-tract) cause the bistability in DNA bending [10-12]. In studied DNA the portion with A-tract alter with the DNA portions with the averaged sequence of the base pairs. As supposed, the A-tract have two possible conformations: one conformation that is the same as for whole macromolecule, and another conformation that differs from the remainder part of double helix. Under some conditions the A-tracts transit to another form, and this is considered as the reason of DNA bending [10].

The observed DNA bending [10,11] may be explained with the help of the results of the present modeling also. According to the case of two equivalent states in the monomer link the bending of DNA fragment is the result of the transition from one state to another.

It is essential that the static excitation in the internal component (43) provides the external component bending to one side for both type (there and back) of transitions (Fig. 4b). Therefore, the alternating of the forms in the internal component leads to the bending to the side of one groove of the macromolecule. If the length of the excitation is divisible to the helix step then the bending of the macromolecule as a whole would realize in one side and in one plane. Such mechanism of the intrinsically bending of DNA is in an agreement with the observed properties of the bent macromolecule [10-12,69].

V. CONCLUSIONS

The performed study shows the possibility of constructing the relatively simple, two-component models for the description of DNA structure transformations on the mesoscopic scales. As was seen for a number of conformational transformations in the frame of the double-helical state the model may be formulated in unifying form. It was shown that on the pathways of the mesoscopic transformations the DNA macromolecule behaves as homogeneous system in the heterogeneous potential field.

The comparison of the static excitations obtained in the constructed models with the observed deformations of the DNA fragments show the qualitative agreement between the theory and experiment. From this correlation the conclusion follows that the observed DNA deformations occasioned by intrinsical localized excitations – static conformational solitons by their nature. The obtained results may be considered as the direct evidence of the localized excitations existence in DNA macromolecule.

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TABLE I. The parameters of the four-mass model

Nucleo- side	m_i^* (<i>a.u.m.</i>)	M_i (<i>a.u.m.</i>)	l_0 (Å)	Θ_0 (degr.)
Ade	203(134)	312	5.1	25
Thy	194(125)	303	4.6	35
Gua	219(150)	328	5.4	23
Cyt	179(110)	288	4.5	30

* In the bracket there are the masses of the nucleic bases.

TABLE II. The model parameters for conformational transition in DNA

Base pair	M (<i>a.u.m.</i>)	m (<i>a.u.m.</i>)	μ_p (<i>a.u.m.</i>)	μ_q (<i>a.u.m.</i>)	I_{0Z} ($10^{-37}\text{g}\cdot\text{cm}^2$)
A·T	615	140.7	99.2	54.5	33.7
G·C	616	140.8	98.5	54.5	34.5

TABLE III. The model parameters for DNA opening

Base pair	M (<i>a.u.m.</i>)	μ (<i>a.u.m.</i>)	J ($10^{-37}\text{g}\cdot\text{cm}^2$)	j ($10^{-37}\text{g}\cdot\text{cm}^2$)
A·T	615	153.7	5.51	1.36
G·C	616	153.4	5.80	1.38

FIGURE CAPTIONS

Fig. 1. The four-mass model for the DNA monomer link: (a) – the fragment of the polynucleotide chain and a pendulum-nucleoside construction, the nucleoside is shown by the dot-dash line, * - the center of masses of nucleoside; (b) – the masses displacements in the plane of the complementary pair; (c) – the double chain of the nucleosides and backbone groups masses.

Fig. 2. A sample view of the potential functions $\Phi(r)$ and $F(r)$: (a) – the case of the double well with non-equivalent stable states; (b) – the case of the equivalent states.

Fig. 3. Static excitation in the case of non-equivalent stable states for DNA monomer link: (a) – the view of the effective potential; (b) – the form of the excitations for internal and external components.

Fig. 4. Static excitation in the case of two equivalent states for DNA monomer link: (a) – the view of the effective potential; (b) – the form of the excitations for internal and external components.







